Clinical trial results:
A Phase III, Randomized, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of MK-3641, a Ragweed (Ambrosia artemisiifolia) Sublingual Immunotherapy Tablet, in Children With a History of Ragweed-Induced Rhinoconjunctivitis With or Without Asthma

Summary

EudraCT number	2014-004341-27
Trial protocol	HU HR Outside EU/EEA
Global end of trial date	19 November 2018

Results information

Result version number	v2 (current)
This version publication date	06 September 2019
First version publication date	31 May 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	3641-008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02478398
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07330
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001881-PIP01-15
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 November 2018
Global end of trial reached?	Yes
Global end of trial date	19 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the efficacy and safety of MK-3641 (short ragweed [Ambrosia artemisiifolia] extract, MK-3641, SCH 039641, RAGWITEK™) sublingual immunotherapy tablets in children aged 5 to 17 years with ragweed-induced allergic rhinitis/rhinoconjunctivitis with or without asthma. The primary hypothesis of this study is that administration of MK-3641 sublingual immunotherapy tablets to children 5 to 17 years of age, compared with placebo, will result in a significant reduction in the combination of rhinoconjunctivitis symptoms and medication use over the peak ragweed season (RS).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy:

Only those participants with ragweed pollen-induced rhinoconjunctivitis with or without controlled asthma were eligible for participation in this study. Participants with asthma may have used as-needed short-acting beta2-agonists (SABAs) and/or low or medium daily doses of inhaled corticosteroids (ICS).

Evidence for comparator: -

Actual start date of recruitment	20 July 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 246
Country: Number of subjects enrolled	Croatia: 79
Country: Number of subjects enrolled	Hungary: 145
Country: Number of subjects enrolled	Serbia: 161
Country: Number of subjects enrolled	Ukraine: 185
Country: Number of subjects enrolled	United States: 209
Worldwide total number of subjects	1025
EEA total number of subjects	224

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	410
Adolescents (12-17 years)	606
Adults (18-64 years)	9
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who were 17 years old at screening and who turned 18 years old prior to randomization were permitted to continue in the study.

Period 1

Period 1 title	Randomization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Short ragweed pollen allergen extract

Arm description:

Participants randomized to short ragweed pollen allergen extract sublingual tablet, to be administered once daily (QD) for up to 35 weeks.

Arm type	Experimental
Investigational medicinal product name	Short ragweed pollen allergen extract
Investigational medicinal product code	
Other name	SCH 03 9641 (MK-3641)
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

One short ragweed pollen allergen extract sublingual tablet, administered once daily (QD) for up to 35 weeks.

Investigational medicinal product name	Loratadine
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Syrup, Tablet
Routes of administration	Oral use

Dosage and administration details:

Loratadine syrup 1 mg/mL, administered as needed for rhinoconjunctivitis symptoms as 5 mL QD for 5-year-old participants and 10 mL QD for 6- to 17-year-old participants, or loratadine tablet (5 mg or 10 mg) administered as one 5 mg tablet QD for 5-year-old participants and one 10 mg tablet QD for 6- to 17-year-old participants

Investigational medicinal product name	Olopatadine
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Eye drops
Routes of administration	Ophthalmic use

Dosage and administration details:

Olopatadine ophthalmic solution 0.1%, administered as needed for rhinoconjunctivitis symptoms as one drop in each affected eye twice daily

Investigational medicinal product name	Mometasone
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Nasal spray

Routes of administration	Intranasal use

Dosage and administration details:

Mometasone furoate nasal spray 50 mcg, administered as needed for rhinoconjunctivitis symptoms as one spray in each nostril QD for 5- to 11- year old participants and or as two sprays in each nostril for 12- to 17-year-old participants

Investigational medicinal product name	Epinephrine
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Self-injectable epinephrine, administered as needed for severe allergic reactions at suggested doses of 15-30 kg for participants weighing 33-66 pounds (0.15 mg) or ≥30 kg for participants weighing ≥66 pounds (0.3 mg). Epinephrine was only provided in countries/study sites where it was a regulatory requirement.

Investigational medicinal product name	Albuterol/Salbutamol
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Albuterol metered-dose inhaler (90 mcg/puff); salbutamol metered-dose inhaler (100 mcg/puff) administered as needed as asthma rescue medication for those participants with asthma

Arm title	Placebo

Arm description:

Participants randomized to placebo sublingual tablet, to be administered QD for up to 35 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

One placebo sublingual tablet, administered QD for up to 35 weeks

Investigational medicinal product name	Loratadine
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Syrup, Tablet
Routes of administration	Oral use

Dosage and administration details:

Loratadine syrup 1 mg/mL, administered as needed for rhinoconjunctivitis symptoms as 5 mL QD for 5-year-old participants and 10 mL QD for 6- to 17-year-old participants, or loratadine tablet (5 mg or 10 mg) administered as one 5 mg tablet QD for 5-year-old participants and one 10 mg tablet QD for 6- to 17-year-old participants

Investigational medicinal product name	Olopatadine
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Eye drops
Routes of administration	Ophthalmic use

Dosage and administration details:

Olopatadine ophthalmic solution 0.1%, administered as needed for rhinoconjunctivitis symptoms as one drop in each affected eye twice daily

Investigational medicinal product name	Mometasone
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

Mometasone furoate nasal spray 50 mcg, administered as needed for rhinoconjunctivitis symptoms as one spray in each nostril QD for 5- to 11- year old participants and or as two sprays in each nostril for 12- to 17-year-old participants

Investigational medicinal product name	Epinephrine
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Self-injectable epinephrine, administered as needed for severe allergic reactions at suggested doses of 15-30 kg for participants weighing 33-66 pounds (0.15 mg) or ≥30 kg for participants weighing ≥66 pounds (0.3 mg). Epinephrine was only provided in countries/study sites where it was a regulatory requirement.

Investigational medicinal product name	Albuterol/Salbutamol
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Albuterol metered-dose inhaler (90 mcg/puff); salbutamol metered-dose inhaler (100 mcg/puff) administered as needed as asthma rescue medication for those participants with asthma

Number of subjects in period 1	Short ragweed pollen allergen extract	Placebo
Started	513	512
Completed	512	510
Not completed	1	2
Withdrawal By Parent/Guardian	-	2
Protocol deviation	1	-

Period 2

Period 2 title	Treatment
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

A double-blind/masking technique was used. Short ragweed pollen allergen extract and placebo were packaged identically so blind/masking was maintained. The participant/parent/guardian and the investigator were unaware of the group assignments.

Arms

Are arms mutually exclusive?	Yes
Arm title	Short ragweed pollen allergen extract

Arm description:

One short ragweed pollen allergen extract sublingual tablet, once daily (QD) for up to 35 weeks.

Arm type	Experimental
Investigational medicinal product name	Short ragweed pollen allergen extract
Investigational medicinal product code	
Other name	SCH 03 9641 (MK-3641)
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

One short ragweed pollen allergen extract sublingual tablet, administered once daily (QD) for up to 35 weeks.

Investigational medicinal product name	Loratadine
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Syrup, Tablet
Routes of administration	Oral use

Dosage and administration details:

Loratadine syrup 1 mg/mL, administered as needed for rhinoconjunctivitis symptoms as 5 mL QD for 5-year-old participants and 10 mL QD for 6- to 17-year-old participants, or loratadine tablet (5 mg or 10 mg) administered as needed for rhinoconjunctivitis symptoms as one 5 mg tablet QD for 5-year-old participants and one 10 mg tablet QD for 6- to 17-year-old participants

Investigational medicinal product name	Olopatadine
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Eye drops
Routes of administration	Ophthalmic use

Dosage and administration details:

Olopatadine ophthalmic solution 0.1%, administered as needed for rhinoconjunctivitis symptoms as one drop in each affected eye twice daily

Investigational medicinal product name	Mometasone
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

Mometasone furoate nasal spray 50 mcg, administered as needed for rhinoconjunctivitis symptoms as one spray in each nostril QD for 5- to 11- year old participants and or as two sprays in each nostril for 12- to 17-year-old participants

Investigational medicinal product name	Epinephrine
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Self-injectable epinephrine, administered as needed for severe
allergic reactions at suggested doses of 15-30 kg for participants weighing 33-66 pounds (0.15 mg) or ≥30 kg for participants weighing ≥66 pounds (0.3 mg). Epinephrine was only provided in countries/study sites where it was a regulatory requirement.

Investigational medicinal product name	Albuterol/Salbutamol
Investigational medicinal product code	
Other name	Rescue therapy

Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Albuterol metered-dose inhaler (90 mcg/puff); salbutamol metered-dose inhaler (100 mcg/puff) administered as needed as
asthma rescue medication for those participants with asthma

Arm title	Placebo

Arm description:

Participants received one placebo sublingual tablet, QD for up to 35 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

One placebo sublingual tablet, administered QD for up to 28 weeks

Investigational medicinal product name	Loratadine
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Syrup, Tablet
Routes of administration	Oral use

Dosage and administration details:

Loratadine syrup 1 mg/mL, administered as needed for rhinoconjunctivitis symptoms as 5 mL QD for 5-year-old participants and 10 mL QD for 6- to 17-year-old participants, or loratadine tablet (5 mg or 10 mg) administered as one 5 mg tablet QD for 5-year-old participants and one 10 mg tablet QD for 6- to 17-year-old participants

Investigational medicinal product name	Olopatadine
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Eye drops
Routes of administration	Ophthalmic use

Dosage and administration details:

Olopatadine ophthalmic solution 0.1%, administered as needed for rhinoconjunctivitis symptoms as one drop in each affected eye twice daily

Investigational medicinal product name	Mometasone
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Nasal spray
Routes of administration	Intranasal use

Dosage and administration details:

Mometasone furoate nasal spray 50 mcg, administered as needed for rhinoconjunctivitis symptoms as one spray in each nostril QD for 5- to 11- year old participants and or as two sprays in each nostril for 12- to 17-year-old participants

Investigational medicinal product name	Epinephrine
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Self-injectable epinephrine, administered as needed for severe allergic reactions at suggested doses of 15-30 kg for participants weighing 33-66 pounds (0.15 mg) or ≥30 kg for participants weighing ≥66 pounds (0.3 mg). Epinephrine was only provided in countries/study sites where it was a regulatory requirement.

Investigational medicinal product name	Albuterol/Salbutamol
Investigational medicinal product code	
Other name	Rescue therapy
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Albuterol metered-dose inhaler (90 mcg/puff); salbutamol metered-dose inhaler (100 mcg/puff) administered as needed as
asthma rescue medication for those participants with asthma

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 2 was defined as the Baseline period for the study.

Number of subjects in period 2[2]	Short ragweed pollen allergen extract	Placebo
Started	512	510
Completed	461	491
Not completed	51	19
Withdrawal By Participant	10	4
Adverse event, non-fatal	20	5
Withdrawal By Parent/Guardian	9	4
Non-Compliance With Study Drug	5	1
Lost to follow-up	5	4
Protocol deviation	2	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of participants globally enrolled was greater than the number of participants who received treatment and entered the baseline period. Period 2 was the Baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Short ragweed pollen allergen extract
Reporting group description:	
One short ragweed pollen allergen extract sublingual tablet, once daily (QD) for up to 35 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received one placebo sublingual tablet, QD for up to 35 weeks.	

Reporting group values	Short ragweed pollen allergen extract	Placebo	Total
Number of subjects	512	510	1022
Age Categorical Units: Subjects			
< 12 years	206	204	410
≥ 12 years	306	306	612
Age Continuous Units: years			
arithmetic mean	12.1	12.2	
standard deviation	± 3.2	± 3.1	-
Gender Categorical Units: Subjects			
Female	188	191	379
Male	324	319	643
Race Units: Subjects			
White	473	477	950
Black or African American	18	14	32
Asian	4	6	10
Native Hawaiian or Other Pacific Islander	3	2	5
American Indian or Alaska Native	1	0	1
Multiple	13	11	24
Ethnicity Units: Subjects			
Hispanic or Latino	15	21	36
Not Hispanic or Latino	490	483	973
Not Reported	4	5	9
Unknown	3	1	4
Baseline Asthma Status Units: Subjects			
Yes	219	217	436
No	293	293	586

End points

End points reporting groups

Reporting group title	Short ragweed pollen allergen extract
Reporting group description:	
Participants randomized to short ragweed pollen allergen extract sublingual tablet, to be administered once daily (QD) for up to 35 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to placebo sublingual tablet, to be administered QD for up to 35 weeks.	
Reporting group title	Short ragweed pollen allergen extract
Reporting group description:	
One short ragweed pollen allergen extract sublingual tablet, once daily (QD) for up to 35 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received one placebo sublingual tablet, QD for up to 35 weeks.	
Subject analysis set title	Short ragweed pollen allergen extract
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants randomized to short ragweed pollen allergen extract sublingual tablet, to be administered once daily (QD) for up to 35 weeks.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants randomized to placebo sublingual tablet, to be administered once daily (QD) for up to 35 weeks.	

Primary: Total Combined Score (TCS) During the Peak Ragweed Season (RS)

End point title	Total Combined Score (TCS) During the Peak Ragweed Season (RS)
End point description:	
TCS is daily symptom score (DSS) plus daily medication score (DMS), assessed in the peak RS (15 consecutive RS days with the highest 15-day average pollen count). The rhinoconjunctivitis (RC) DSS assesses 6 allergy symptoms measured on a scale of 0 to 3 (0=no symptoms, 3=severe symptoms; score range: 0-18). Lower DSS indicates less RC symptoms. The RC DMS is based on use of RC rescue medications (loratadine, olopatadine, mometasone), with different rescue medications being assigned different scores/dose unit (score range: 0-20). Lower DMS indicates less RC medication use. Summed RC DSS+DMS ranged from 0 to 38; a lower score indicates less RC symptoms and medication use. Components that contribute to DSS and DMS endpoints are collected in an e-diary completed by the participant/parent/guardian. Evaluation is based on average TCS during peak RS. The analysis population includes all treated participants w/ ≥1 e-diary entry for the specified measurement and timeframe.	
End point type	Primary
End point timeframe:	
The 15-day period during the ragweed season with the highest moving pollen average	

End point values	Short ragweed pollen allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	460	487		
Units: Score on a scale				
least squares mean (confidence interval 95%)	4.39 (3.85 to 4.94)	7.12 (6.57 to 7.67)		

Statistical analyses

Statistical analysis title	Comparison of MK-3641 vs Placebo
Statistical analysis description:	
Model included fixed effects of treatment, baseline asthma status, age group, pollen season, and pollen region nested within pollen season	
Comparison groups	Placebo v Short ragweed pollen allergen extract
Number of subjects included in analysis	947
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.45
upper limit	-2

Secondary: Average TCS During the Entire RS

End point title	Average TCS During the Entire RS
End point description:	
TCS is DSS plus DMS, assessed during the entire RS. This starts from the first day of 3 consecutive days w/ ragweed pollen counts ≥10 grains/m^3 through the last day of the last occurrence of 3 consecutive days w/ ragweed pollen counts ≥10 grains/m^3. Duration of entire RS is up to 13 weeks; this duration varies by site/region. The RC DSS assesses 6 allergy symptoms measured on a scale of 0 to 3 (range: 0-18). A lower DSS indicates less RC symptoms. The RC DMS is based on use of RC rescue medications (loratadine, olopatadine, mometasone) w/ different scores/dose unit (range: 0-20). A lower DMS indicates less RC medication use. The sum of RC DSS+DMS ranges from 0 to 38, w/ a lower score indicating less RC symptoms and medication use. Components contributing to the TCS for the entire RS are collected in an e-diary completed by the participant/parent/guardian. The analysis pop. includes all treated participants w/ ≥1 e-diary entry for the specified measurement and timeframe.	
End point type	Secondary
End point timeframe:	
Up to 13 weeks	

End point values	Short ragweed pollen allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	466	491		
Units: Score on a scale				
least squares mean (confidence interval 95%)	3.88 (3.44 to 4.33)	5.75 (5.30 to 6.20)		

Statistical analyses

Statistical analysis title	Comparison of MK-3641 vs Placebo
Statistical analysis description:	
Model included fixed effects of treatment, baseline asthma status, age group, pollen season, and pollen region nested within pollen season	
Comparison groups	Short ragweed pollen allergen extract v Placebo
Number of subjects included in analysis	957
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Difference in LS Mean
Point estimate	-1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.46
upper limit	-1.27

Secondary: Average Rhinoconjunctivitis (RC) DSS During the Peak RS

End point title	Average Rhinoconjunctivitis (RC) DSS During the Peak RS
End point description:	
The DSS consists of a total of 6 rhinoconjunctivitis symptoms: 4 rhinitis symptoms (runny nose, stuffy nose, sneezing, itchy nose) and 2 conjunctivitis symptoms (itchy eyes, watery eyes). The components that contribute to the DSS endpoint are collected in an e-diary completed by the participant/parent/guardian. The RC DSS is measured on a 4-point scale from 0 to 3 as follows: 0 (no sign/symptom evident) to 3 (sign/symptom that is hard to tolerate; may cause interference with activities of daily living and/or sleeping). The maximum DSS is 18 points if a participant experiences all 6 symptoms with an intensity of 3 for each symptom. The minimum DSS is 0 points if a participant experiences no symptoms. A lower DSS means symptoms are less severe. The evaluation is based on the average DSS during the peak RS. The analysis population includes all treated participants w/ ≥1 e-diary entry for the specified measurement and timeframe.	
End point type	Secondary
End point timeframe:	
The 15-day period during the ragweed season with the highest moving pollen average	

End point values	Short ragweed pollen allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	468	494		
Units: Score on a scale				
least squares mean (confidence interval 95%)	2.55 (2.24 to 2.86)	3.95 (3.63 to 4.26)		

Statistical analyses

Statistical analysis title	Comparison of MK-3641 vs Placebo
Statistical analysis description:	
Model included fixed effects of treatment, baseline asthma status, age group, pollen season, and pollen region nested within pollen season	
Comparison groups	Short ragweed pollen allergen extract v Placebo
Number of subjects included in analysis	962
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.81
upper limit	-0.99

Secondary: Average Rhinoconjunctivitis (RC) DMS During the Peak RS

End point title	Average Rhinoconjunctivitis (RC) DMS During the Peak RS
End point description:	
This DMS endpoint consists of a total of scores for use of RC medications: loratadine syrup or tablets (6 points), olopatadine (6 points), and mometasone (8 points). The score range of the RC DMS is 0-20 points, and a lower DMS means that less medication is used. The method used for analysis of the RC DMS is a zero-inflated log-normal model, which takes the average RC DMS during the peak RS as the response and adjusts for the same terms as in the ANOVA model. The components that contribute to the DMS endpoint are collected in an e-diary completed by the participant/parent/guardian. The analysis population includes all treated participants w/ ≥1 e-diary entry for the specified measurement and timeframe.	
End point type	Secondary
End point timeframe:	
The 15-day period during the ragweed season with the highest moving pollen average	

End point values	Short ragweed pollen allergen extract	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	460	487		
Units: Score on a scale				
arithmetic mean (confidence interval 95%)	2.01 (1.57 to 2.46)	3.85 (3.14 to 4.57)		

Statistical analyses

Statistical analysis title	Comparison of MK-3641 vs Placebo
Statistical analysis description:	
Model included fixed effects of treatment, baseline asthma, age group, pollen season, and pollen region nested within pollen season	
Comparison groups	Short ragweed pollen allergen extract v Placebo
Number of subjects included in analysis	947
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Zero-Inflated Log-Normal Model
Parameter estimate	Mean difference (final values)
Point estimate	-1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	-1.08

Secondary: Percentage of Participants Reporting Pre-specified Local Application Site Reactions

End point title	Percentage of Participants Reporting Pre-specified Local Application Site Reactions
End point description:	
Pre-specified local application site reactions, irrespective of causality, included AEs related to lip swelling/edema, mouth swelling/edema, palatal swelling/edema, swollen tongue/edema, oropharyngeal swelling/edema, pharyngeal edema/throat tightness, oral pruritus, throat irritation, tongue pruritus, and ear pruritus. The safety population was all participants as treated. One participant was randomized to placebo but received short ragweed pollen allergen extract for one day and is included in the short ragweed pollen allergen extract arm.	
End point type	Secondary
End point timeframe:	
Up to 35 weeks	

End point values	Short ragweed pollen allergen extract	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	513	509		
Units: Percentage of participants				
number (not applicable)	64.52	26.92		

Statistical analyses

Statistical analysis title	Difference in %
Comparison groups	Short ragweed pollen allergen extract v Placebo
Number of subjects included in analysis	1022
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Difference in % estimates
Point estimate	37.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.82
upper limit	43.12

Secondary: Percentage of Participants Reporting Anaphylaxis and/or Systemic Allergic Reactions

End point title	Percentage of Participants Reporting Anaphylaxis and/or Systemic Allergic Reactions

End point description:

For the purposes of this study, systemic allergic reactions are allergic reactions that occur away from the site of study drug application (allergic reactions other than local application site reactions). Anaphylaxis is a severe allergic reaction that typically involves more than one body system. The safety population was all participants as treated. One participant was randomized to placebo but received short ragweed pollen allergen extract for one day and is included in the short ragweed pollen allergen extract arm.

End point type	Secondary

End point timeframe:

Up to 35 weeks

End point values	Short ragweed pollen allergen extract	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	513[1]	509[2]		
Units: Percentage of participants				
number (not applicable)	0.58	0.20		

Notes:

[1] - No participants reported anaphylaxis. All reported events were systemic allergic reactions.

[2] - No participants reported anaphylaxis. All reported events were systemic allergic reactions.

Statistical analyses

Statistical analysis title	Difference in %
Comparison groups	Short ragweed pollen allergen extract v Placebo
Number of subjects included in analysis	1022
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.32
Method	Miettinen & Nurminen
Parameter estimate	Difference in % estimates
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	1.53

Secondary: Percentage of Participants Treated with Epinephrine

End point title	Percentage of Participants Treated with Epinephrine

End point description:

Self-injectable epinephrine was provided to each participant/parent/guardian at randomization in countries where it is a regulatory requirement, and was to be available around the time treatment is administered at home. Self-injectable epinephrine was intended for immediate self-administration for an anaphylactic reaction, including symptoms/signs of upper airway obstruction. Instances of treatment with forms of epinephrine other than systemic epinephrine (e.g., inhaled racepinephrine) were counted as use of epinephrine. The safety population was all participants as treated. One participant was randomized to placebo but received short ragweed pollen allergen extract for one day and is included in the short ragweed pollen allergen extract arm.

End point type	Secondary

End point timeframe:

Up to 35 weeks

End point values	Short ragweed pollen allergen extract	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	513[3]	509		
Units: Percentage of participants				
number (not applicable)	0.19	0.20		

Notes:

[3] - Participant in this arm received inhaled racepinephrine

Statistical analyses

Statistical analysis title	Difference in %
Comparison groups	Short ragweed pollen allergen extract v Placebo
Number of subjects included in analysis	1022
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.996
Method	Miettinen & Nurminen
Parameter estimate	Difference in % estimates
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.92
upper limit	0.92

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 35 weeks

Adverse event reporting additional description:

An AE is any physical or clinical change or disease experienced by the participant any time during the study, whether or not considered related to use of the study drug. The safety population was all participants as treated. 1 participant was randomized to pbo but received short ragweed pollen allergen extract for 1 day and is included in that arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants who received placebo sublingual tablet, administered once daily (QD) for up to 35 weeks.

Reporting group title	Short ragweed pollen allergen extract

Reporting group description:

Participants who received short ragweed pollen allergen extract sublingual tablet, administered once daily (QD) for up to 35 weeks.

Serious adverse events	Placebo	Short ragweed pollen allergen extract	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 509 (1.77%)	7 / 513 (1.36%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 509 (0.00%)	1 / 513 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	1 / 509 (0.20%)	0 / 513 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			

subjects affected / exposed	0 / 509 (0.00%)	1 / 513 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 509 (0.20%)	1 / 513 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 509 (0.20%)	0 / 513 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral pruritus			
subjects affected / exposed	0 / 509 (0.00%)	1 / 513 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 509 (0.59%)	0 / 513 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Conduct disorder			
subjects affected / exposed	1 / 509 (0.20%)	0 / 513 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 509 (0.00%)	1 / 513 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			

subjects affected / exposed	0 / 509 (0.00%)	1 / 513 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 509 (0.20%)	0 / 513 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 509 (0.20%)	0 / 513 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral inection			
subjects affected / exposed	0 / 509 (0.00%)	1 / 513 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Short ragweed pollen allergen extract	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	233 / 509 (45.78%)	370 / 513 (72.12%)	
Nervous system disorders			
Headache			
subjects affected / exposed	49 / 509 (9.63%)	45 / 513 (8.77%)	
occurrences (all)	67	100	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	20 / 509 (3.93%)	29 / 513 (5.65%)	
occurrences (all)	23	33	
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	35 / 509 (6.88%)	177 / 513 (34.50%)	
occurrences (all)	65	750	
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	30 / 509 (5.89%)	54 / 513 (10.53%)	
occurrences (all)	53	119	
Diarrhoea			
subjects affected / exposed	21 / 509 (4.13%)	26 / 513 (5.07%)	
occurrences (all)	29	55	
Enlarged uvula			
subjects affected / exposed	2 / 509 (0.39%)	33 / 513 (6.43%)	
occurrences (all)	2	65	
Glossodynia			
subjects affected / exposed	13 / 509 (2.55%)	64 / 513 (12.48%)	
occurrences (all)	29	171	
Lip swelling			
subjects affected / exposed	7 / 509 (1.38%)	66 / 513 (12.87%)	
occurrences (all)	14	165	
Nausea			
subjects affected / exposed	43 / 509 (8.45%)	70 / 513 (13.65%)	
occurrences (all)	69	167	
Oral pain			
subjects affected / exposed	16 / 509 (3.14%)	64 / 513 (12.48%)	
occurrences (all)	29	151	
Oral pruritus			
subjects affected / exposed	62 / 509 (12.18%)	247 / 513 (48.15%)	
occurrences (all)	131	1115	
Stomatitis			
subjects affected / exposed	6 / 509 (1.18%)	34 / 513 (6.63%)	
occurrences (all)	13	89	
Swollen tongue			
subjects affected / exposed	4 / 509 (0.79%)	56 / 513 (10.92%)	
occurrences (all)	5	132	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	30 / 509 (5.89%)	30 / 513 (5.85%)	
occurrences (all)	53	39	
Oropharyngeal pain			

subjects affected / exposed	29 / 509 (5.70%)	25 / 513 (4.87%)	
occurrences (all)	44	56	
Pharyngeal oedema			
subjects affected / exposed	8 / 509 (1.57%)	58 / 513 (11.31%)	
occurrences (all)	14	138	
Throat irritation			
subjects affected / exposed	98 / 509 (19.25%)	254 / 513 (49.51%)	
occurrences (all)	223	1048	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	36 / 509 (7.07%)	38 / 513 (7.41%)	
occurrences (all)	50	50	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 September 2016	The asthma DSS will be completed daily beginning with Visit 4 by all participants in the study, and decreased blood volume is to be taken at screening
11 September 2018	Addition of "severe asthma exacerbation" to the list of discontinuation criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported